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What is the meaning of “small-fiber polyneuropathy” in fibromyalgia? An alternate answer

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Clauw makes several compelling points in his Commentary² about the significance of the manuscript of Doppler et al.³ and the dozen others that report objective evidence of small-fiber polyneuropathy (SFPN) in roughly half of patients with the multi-symptom syndrome classically known as fibromyalgia syndrome (FMS). He rightly asserts that the association between FMS and SFPN is now proven, so it is time to consider its significance. This finding is important since fibromyalgia affects several percent of the population.²³ One caution concerns the differences in axonal caliber between FMS and SFPN reported by Doppler et al.³ The medical and scientific significance of these differences is currently unknown, so they do not detract from the disruptive discovery of reduced intraepidermal nerve fiber density (IENFD) in fibromyalgia.^{5,9,13,14,22} A “disruptive discovery” is one that is ground breaking – overturning established concepts and forcing widespread changes in practice. As discussed by Scientific American,¹⁹ the finding of abnormal skin biopsies consistent with SFPN in some FMS patients is the first pathology confirmed for FMS. It rescues at least some FMS patients from the nonproductive “functional illness” label and offers new treatment possibilities. Informed FMS patients are already seeking evaluations for small-fiber polyneuropathy, causing bottlenecks for some neurology practices.

I hope to clarify a few misinterpretations. One is that “decreases in IENFD have been noted in most chronic pain conditions”.² Actually, ENF have not yet been quantitated in most non-neuropathic pain conditions. Clauw also suggests that reduced IENFD in “non-pain” disorders such as postural orthostatic tachycardia syndrome (POTS) and amyotrophic lateral sclerosis (ALS) invalidate the specificity of the fibromyalgia findings.² He also makes the converse statement that the non-pain symptoms of fibromyalgia can’t possibly be caused by SFPN. These views may reflect the all-too-common unawareness of the diverse functions of small fibers. In fact, these unmyelinated and thinly myelinated axons innervate and modulate

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almost every organ and tissue including the “deeper proximal structures and even visceral organs” that Clauw references.² Because of the protean somatic and autonomic effects mediated by these omni-functional neurons, pain is only one among many symptoms of SFPN, and some patients with SFPN do not have chronic pain.¹¹ And since physiologic data link more than 50% of POTS cases to SFPN,²⁰ the POTS example seems invalid. Dysautonomic symptoms are just as characteristic of SFPN as pain. For instance, 80% of SFPN patients have abnormal results of sweat testing, and 75% have reduced heart-rate variability.²¹

Pathological studies also prove that small-fiber axonopathy causes abnormal innervation and malfunction of the body’s small blood vessels. This neurogenic microvasculopathy is a likely explanation for the muscle hypoperfusion, deep pain, and exercise intolerance characteristic not only of fibromyalgia but also of SFPN.^{1,4} Unexpectedly, the vascular dysregulation so characteristic of POTS/SFPN is able to impair higher cortical function by decreasing cerebral blood flow.¹⁵ These small-fiber mediated effects on the brain offer a new biologically plausible explanation for FMS-associated “brain fog”.¹⁸ They suggest the need to test whether “brain fog” in FMS patients with SFPN microvasculopathy can be treated using the strategies for improving brain perfusion in POTS and SFPN. These include expanding blood volume by augmenting salt and fluid consumption, reducing blood pooling in the legs with exercise and compression stockings, and treatment with midodrine or fludrocortisone.¹⁶

A minor disagreement is with the Commentary’s statement that there is no correlation between the severity of IENFD and the presence or absence of neuropathic pain.² Although this is often true, my group reported a very tight correlation between the severity of loss of IENF and the presence or absence of postherpetic neuralgia pain after shingles.¹² A significant correlation has also been documented in acute motor Guillain-Barré syndrome,¹⁷ identifying another “non-pain disorder” that includes previously unappreciated neuropathic pain and small-fiber axonopathy.

Clauw states that there is “overwhelming evidence that the CNS is playing the major pathogenic role in FMS,”² but then he confusingly attributes these changes “(usually but not always atrophy) in the size and shape of brain regions involved in pain processing”² to secondary neuroplasticity rather than primary “encephalopathy”.² As a neurologist, I agree that brain plasticity contributes to FMS symptoms, but I believe it is unlikely to have “the major pathogenic role”.² Clauw himself demonstrated that changes in the brain cortex of fibromyalgia patients are not primary, but rather secondary to their accompanying affective disorders.⁸ Thus, these brain changes cannot be the root cause of these patients’ fibromyalgia. The mechanisms of the entrainment of the brain by small fibers are emerging, with C- and A-fibers now shown to control central pain amplification in humans.⁶ And in “classical” SFPN, the severity of small-fiber loss predicts the severity of reduced functional connectivity between the anterior cingulate cortex and the amygdala and precuneus.⁷ Many peripheral pain syndromes, including dysmenorrhea in normal women, also produce brain imaging changes,¹⁰ but surely no one believes that the brain is the primary cause of either SFPN or dysmenorrhea?

Clauw correctly states that “any pain clinician will accept the use of the term SFN when an individual presents with classic distal neuropathic pain and has evidence of classic findings of decreased IENFD”² but he downplays the new links between decreased IENFD and fibromyalgia. I prefer an alternate interpretation – that the signs and symptoms of SFPN are far broader than classically defined, and SFPN is turning out to be more common than we knew. The discovery that SFPN contributes to some cases of FMS offers us a chance to update entrenched archaic definitions of both SFPN and FMS. Disease definitions require regular updates to incorporate new discoveries. This benefits not only the patients, but also clinicians and scientists. Fibromyalgia is long overdue.

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